UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,003	11/26/2003	Jing Ma	549062000200	9567

30542 7590 03/28/2007

FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,003	MA ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,35,36,40,41,47 and 50-67* is/are pending in the application.

4a) Of the above claim(s) *18,40,41 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-23,35,36 and 50-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

LAB

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-23, 35, 36, 40, 41, 47 and 50-67 are all the pending claims for this application.

2. Claims 1, 6, 21-23, 36, 56 and 57 have been amended, claims 37-39, 42-46, 48 and 49 have been canceled and new claims 58-67 have been added by the Response of 1/18/07. The amendments to the claims and the new claims have been considered and entered.

3. Claims 18, 40, 41 and 47 are withdrawn.

4. Claims 1-17, 19-23, 35, 36 and 50-67 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for rejection.

Objections Withdrawn

Sequence Compliance

6. The revised Sequence Listing (along with the CRF and statement) providing a sequence identifier for the sequences, gca Ctc gag ttt tac Ccg gag Ka ggg aga g and gag ccc aaa tct tgt gac aaa ac, disclosed at p. 41, [0163], lines 8 and 9 of the specification is acknowledged and obviates the objection.

Specification

7. The objection to the abstract of the disclosure is withdrawn in view of Applicant's arguments on p. 12 of the Response of 1/18/07.

8. The objections to the specification are withdrawn for the following reasons:

a) the deposit information for the plasmids on p. 5, [0013], line 5 has been deleted and obviates the objection;

b) the sequence, $(Gly_4Ser)_3$, on p. 21, [0108], line 5; p. 52, [0193], line 5 and [0195], line 4, has been identified by SEQ ID NO:6 pursuant to 37 CFR 1.821;

c) the sequences on p. 41, [0163], lines 8 and 9 has been identified by sequence identifier (SEQ ID NO: 69 and 70) pursuant to 37 CFR 1.821;

d) the term "proteinuous" has been amended to -- proteinaceous -- throughout the specification and the abstract

Claims

9. The objections to Claims 16, 21, 22, 23, 52, 56 and 57 are withdrawn for the following reasons:

a) The non-elected subject matter for species of antibody in Claims 16 and 52 is withdrawn from consideration.

b) Claims 21 and 56 have been amended to replace "is" with -- are -- .

c) The term recite "(Gly4Ser)3" in Claims 22 and 57 has been amended to recite "$(G1y_4Ser)_3$" as set forth in the specification and to include the sequence identifier SEQ ID NO:6.

d) The non-elected subject matter for SEQ ID NOS: 44, 46, 48, 58, 60, 62, 64, 66 and 68 for Claim 23 is withdrawn from consideration.

e) Claim 57 has been amended to depend from Claim 56.

Applicant's comments on pp. 12-13 of the Response of 1/18/07 with respect to the claim objections are acknowledged.

Objections Maintained

Drawings

10. The objection to Figures 6 and 7; Figures 23 and 24; Figures 31 and 32; and Figures 53, 54 and 55 for being on the same page is maintained. Applicant's request on p. 11 of the Response of 1/18/07 for a deferral in filing revised drawings until the application is in condition for allowance is acknowledged.

Withdrawal of Rejections

Claims - 35 USC § 112, second paragraph

11. The rejection of Claim 6 in lacking antecedency for the limitation "the mammalian Flt3 ligand" is withdrawn in view of the amendment of the claim to depend from Claim 5, and further in view of Applicant's comments on p. 14 of the Response 1/18/07.

12. The rejection of Claim 21 in lacking antecedency for the limitation "the targeting agent" is withdrawn in view of the claim being amended to recite "tumoricidal agent", and further in view of Applicant's comments on p. 14 of the Response 1/18/07.

13. The rejection of Claim 36 for the recitation "an effective amount of a chimeric protein" as the product is a kit, and the kit is not limited by an intended use, is withdrawn in view the claim being amended to a kit for treating a neoplasm in a mammal, and further in view of Applicant's comments on p. 14 of the Response 1/18/07.

Claims - 35 USC § 112, first paragraph

Enablement

14. The rejection of Claim 23 under 35 U.S.C. 112, first paragraph, in lacking enablement for making or using a chimeric protein comprising an antibody with only a single VH domain (SM5.1/Flt3 ligand chimeric proteins of SEQ ID NOS: 24 (huSMVH/Fc/FL), 26 (huSMVH/Fc/Link/FL), 30 (chSMVH/Fc/FL), and 32 (chSMVH/Fc/Link/FL)) is withdrawn with respect to the deletion of these sequences from the claim and further in view of Applicant's comments on p. 17 of the Response of 1/18/07.

Claims - 35 USC § 102

15. The rejection of Claims 1-5 and 20 under 35 U.S.C. § 102(b) as being anticipated by Wang et al. (Chinese Micro. & Immunol. J. 20(5):397-401 (2000)) as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000)) is withdrawn.

Applicant's arguments, see p. 20, filed in the Response of 1/18/07, with respect to Wang have been fully considered and are persuasive. Applicant's allege that the

proteins of Wang are individually but simultaneously expressed, and are not chimeric proteins.

The Examiner further submits that the IRES gene segment is not expressed as a protein or peptide and does not provide a linker or linking means between the two individual TK and Ftl3 expressed proteins to create a fusion protein.

16. The rejection of Claims 1-5, 14, 15, 17, 19, 20, 35, 36, 50, 51 and 53-55 are rejected under 35 U.S.C. § 102(e) as being anticipated by Tang et al. (USPN 6,783,969) is withdrawn.

Applicant's arguments, see p. 21, filed in the Response of 1/18/07, with respect to Tang have been fully considered and are persuasive. Applicant's allege that Tang discloses several polypeptide sequences having unrelated predicted functions in Table 2, and that the Ftl3 ligand is administered in combination with the polypeptides rather than as part of a fusion construct with any of the polypeptides. The Examiner further submits that in as much as Tang discloses fusion constructs, Ftl 3 ligand is not a portion of the construct per se.

17. The rejection of Claims 1, 16, 50 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (USPN 6,783,969) as applied to claims 1 and 50 above, and further in view of Trefzer et al. (Arch Dermatol. Res. 292:583-589 (2000)) is withdawn.

Applicant's arguments, see p. 22, filed in the Response of 1/18/07, with respect to Tang in view of Trefzer have been fully considered and are persuasive.

18. The rejection of Claims 50 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (USPN 6,783,969) as applied to claim 50, and further in view of Sandee et al. (BMC Biotechnology 2:16-23 (2002)) is withdrawn.

Applicant's arguments, see p. 22, filed in the Response of 1/18/07, with respect to Tang in view of Sandee have been fully considered and are persuasive. The rejection falls because of the Examiner's reconsideration of Claim 50 more especially over the Tang reference.

19. The rejection of Claims 1 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang and Lynch as applied to claim 1, and further in view of Trefzer is withdrawn.

Applicant's arguments, see p. 22, filed in the Response of 1/18/07, with respect to Tang, Lynch and Trefzer have been fully considered and are persuasive. The rejection falls because of the Examiner's reconsideration of Claim 1 more especially over the Tang reference.

Rejections Maintained

Claims - 35 USC § 112, second paragraph

20. The rejection of Claims 1, 8, 9 and 50 for the recitation "biologically active" (Claims 1 and 50) and "substantially retains its biological activity" (Claims 8 and 9) is maintained.

Applicant's arguments on pp. 13-14 of the Response of 1/18/07, that any fragment corresponding to SEQ ID NO:2 having substantial biological activity (at least 50%) is taught by the specification at [0095], have been considered but are not found persuasive.

First, if Applicant's are proposing that the term "substantial" means "at least 50%", then the limitation has not been introduced into any of the claims nor is it read into the claims from the specification. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The Examiner resubmits that generic Claims 1 and 50 are drawn to any Ftl3 ligand known or yet to be discovered at the time the invention was made and/or the application was filed. Inasmuch as the claims encompass the full-length Ftl3 ligand of SEQ ID NO:2 (GenBank Accession No. U03858 (Flt3 ligand available in 1994) or biologically active fragments thereof, the claims are not in any way limited to the Ftl3 ligand of SEQ ID NO:2 much less any other specific Ftl3 ligand. Thus, the claims cover an infinite number of Ftl3 ligands, which possess an infinite and undefined number of biological properties. As written, Claims 1 and 50 are reach-through claims for an indefinite Ftl3 ligand(s).

Absent a showing to the contrary, Applicants specification does not identify a single fragment that meets all of the limitations of Claim 8, namely, a) at least 100 amino acid residues, b) at least 40% identity to the sequence of SEQ ID NO: 2, and c) "substantially retains its biological activity".

As for Claim 9, the Ftl3 ligand is indefinite, and therefore, so is the corresponding biological activity of the ligand. Because the metes and bounds of the Ftl3 ligand are not ascertainable from the specification, so to are the biological properties much less any biological property being "substantially retained." The ligand of Claim 9 is limited to SEQ ID NO:2 by an antibody which binds to the sequence, and that the ligand bind the antibody. Claim 9 is indefinite as to whether the ligand comprises the same sequence or epitope of SEQ ID NO:2 to which the antibody binds. Otherwise, the ligand can bind to any portion of the antibody.

Claims - 35 U.S.C. 112, first paragraph

Written Description

21. The rejection of Claims 1-8, 11, 14-17, 19-22, 35, 36 and 50-57 (and new Claims 58-67) under 35 U.S.C. 112, first paragraph, in lacking written description support for "a FTL3 ligand" is maintained.

Applicant's arguments filed on pp. 14-16 of the Response of 1/18/07 have been fully considered but they are not persuasive. Applicant's allege "the rejection seems to be based on the assertion that no sequences encoding, for example, a chimeric molecule comprising a Flt3 ligand having at least 40% or 80% sequence identity to SEQ

ID NO:2, the full length amino acid sequence o f Flt 3 ligand. However, exemplary sequences are disclosed in the specification and providing sequences of all possible members of a genus is not essential to have a written description of a genus of Flt3 ligand fragment" Applicant's rely on the decisions of Ralston Purina v. Far-Mar and Capon v. Eshhar. Applicants assert that because the full length sequence for the Ftl3 ligand is disclosed as GenBank Accession No. U03858 and one skilled in the art could reasonably interpret the characteristics of the fragments encompassed by a chimeric molecule comprising a Flt3 ligand having at least 40% or 80% sequence identity to SEQ ID NO:2,

First, the Examiner submits that Applicant's do not appear to have understood (or at least did not address) the aspect of the written description rejection, which applies to the infinite scope of Ftl3 ligands encompassed by all of the claims. As discussed supra, the generic claims are directed to any Flt3 ligand where no relevant, identifying structural and functional characteristics are recited in the claims much less taught in the specification that would allow one skilled in the art to reasonably conclude that Applicants were in possession of the Flt3 ligands that are known or yet to be discovered, and which are claimed. Further, because the generic Ftl3 ligand can not be construed from the specification, Applicant's citation of the decisions from Ralston Purina v Far-Mar and Capon v Eshhar are inapplicable as they relate only to sequences that were known in the prior art at the time of application filing. In the instant case, Applicants do not even provide a suggestion much less contemplate what characteristics the genus of Ftl3 ligands should comprise.

Second, the Examiner submits that inasmuch as the full length Ftl3 ligand sequence of SEQ ID NO:2 was known in the art at the time of application filing, and that biologically active fragments could be generated therefrom, the specification does not teach or suggest the infinite number of modifications (i.e., amino acid insertions, deletions, substitutions) or even where theses modifications can be made to in order for fragments to have at least 40% or 80% sequence identity to SEQ ID NO:2. Are there any distinguishing core structures in the Ftl3 ligand sequence of SEQ ID NO:2 that must be retained for biological activity, and if so, what are these structures? None of this disclosed in the specification or claimed. Further the specification does not disclose a "reasonable" number of examples for the species of fragments meeting all of the limitations for Claims 8 and 11.

Enablement

22. The rejection of Claims 1-8, 11, 14-17, 19-22, 35, 36 and 50-57 (and new Claims 58-67) under 35 U.S.C. 112, first paragraph, in lacking enablement for making or using a chimeric protein comprising just any known or yet to be discovered Flt3 ligand moiety fused to just any tumoricidal agent much less a chimeric protein where the biological activity for each of the moieties is retained, is maintained.

Applicant's general arguments on pp. 16-19 of the Response of 1/18/07 have been fully considered but they are not persuasive. Applicant's outlined approach to addressing each of the Wands factors as they would apply to a chimeric protein comprising the full length Ftl3 ligand protein of SEQ ID NO:2 (or biologically active

fragments thereof) and a tumoricidal agent are acknowledged, but do not even begin to address the instant claim scope for just any Ftl3 ligand comprising the chimeric protein. As discussed, supra, under the 112, second paragraph and 112, first paragraph (written description) rejections (and for reasons of record), the instant generic claims 1 and 50 are drawn to a chimeric protein comprising any known or unknown Ftl3 ligand and a tumoricidal agent. Because there is no written description support for the infinite genus of Ftl3 ligands, one skilled in the art would not be enabled to make or use a chimeric protein comprising the infinite genus of Ftl3 ligands as instantly claimed.

Further as applied to Claims 8 and 11 for chimeric proteins comprising Ftl3 ligand fragments having at least 40% or 80% identity to the sequence of SEQ ID NO:2, Applicants have not addressed in their arguments where in the specification or the prior art, one skilled in the art could generate any such fragments without unduly burdensome experimentation. Absent evidence to the contrary, the Examiner understands that the experimentation involved in identifying these fragments would require making processive N-terminal and/or C-terminal deletions of the full length sequence of SEQ ID NO:2 in order obtain contiguous fragments of at least 100 amino acids, and further modifying the fragments to introduce or delete or substitute amino acids or the combination without limitation, and prior to fusing the fragments to the tumoricidal agent, the fragments would then need to be tested in some in vitro or in vivo bioassay to determine whether the fragment had "substantial" biological activity, which in the specification, is defined as at least 50% [0093]. Further recombinant technology would then be required to fuse the selected fragments into a construct comprising the

tumoricidal agent, which would then need to be expressed prior to characterizing the chimeric protein for its Ftl3 ligand properties and tumoricidal properties. The enablement rejection is maintained because of the amount of experimentation and the unpredictability of identifying any chimeric protein, which meets all of the limitations of the claims.

Claims - 35 USC § 102

23. The rejection of Claims 1-7, 19, and 21 under 35 U.S.C. § 102(b) as being anticipated by Wu et al. (Molec. Ther. 3:368-374 (Mar 2001)) as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000)) is maintained.

Applicant's arguments filed on p. 19 of the Response of 1/18/07 have been fully considered but they are not persuasive. Applicant's allege that Wu does not disclose a substantially purified chimeric protein, but expression of a chimeric protein from DNA constructs in cell culture and in mice.

The Examiner submits that because of the indefiniteness of the limitation "substantially purified" in amended Claim 1 as discussed supra, and because the limitation does not impart a patentably distinguishable feature to the claimed chimeric protein, that Wu reads on the instant claims.

24. The rejection of Claims 1, 3-5, 7, and 19 under 35 U.S.C. § 102(b) as being anticipated by Hung et al. (Cancer Research. 61:1080-1088 (February 1, 2001)) as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000)) is maintained.

Applicant's arguments filed on pp. 19-20 of the Response of 1/18/07 have been fully considered but they are not persuasive. Applicant's allege that Hung does not disclose a substantially purified chimeric protein, but expression of a chimeric protein from DNA constructs in cell lines, cultured cells or mice containing such constructs.

The Examiner submits that because of the indefiniteness of the limitation "substantially purified" in amended Claim 1 as discussed supra, and because the limitation does not impart a patentably distinguishable feature to the claimed chimeric protein, that Hung reads on the instant claims.

25. The rejection of Claims 1-6, 14, 15, 20, 35, 50, 51, and 55 are rejected under 35 U.S.C. § 102(b) as being anticipated by Krieg et al. (USPN 6,218,371)) as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000)) is maintained.

Applicant's arguments filed on p. 20 of the Response of 1/18/07 have been fully considered but they are not persuasive. Applicant's allege that Kreig discloses antigen-cytokine fusion proteins, and that the antigen of Kreig cannot be equated with the tumoricidal agent of the instant chimeric protein, because "an antigen merely binds antibody."

The Examiner respectfully disagrees with Applicant's interpretation of Kreig. Kreig discloses antigen-cytokine fusion proteins where the antigen is one where a subject is already exposed to the antigen, and the antigen-fusion protein is administered in an effective amount for inducing a synergistic antigen specific immune response. Kreig discloses proteinaceous tumor antigens for use in the chimeric construct (or the

idiotype of a secreted immunoglobulin serving as the antigen as discussed or record). The antigen portion of the chimeric protein of Kreig, thus serves to enhance an antigen-specific tumoricidal immune response. The Examiner submits that the claims are not drawn to a proteinaceous tumoricidal agent that is distinguished as being directly or indirectly tumoricidal, and therefore, an antigen having an anti-tumor, immune eliciting effect as disclosed in Kreig, would read on the instant claims.

Claims - 35 USC § 103

26. The rejection of Claims 1-7, 10, 12, 13, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (Molec. Ther. 3:368-374 (Mar 2001)) in view of Lynch et al. (US20030113341) is maintained.

Applicant's arguments filed on p. 21-22 of the Response of 1/18/07 have been fully considered but they are not persuasive. Applicant's allege that Wu does not disclose a purified chimeric protein comprising the Ftl3 ligand and a tumoricidal agent, and inasmuch as Lynch discloses fusion proteins, Lynch does not contemplate the Ftl3 ligand.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re*

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, and as discussed supra, the chimeric protein is not patentably distinguishable over Wu, and because Lynch discloses the properties of the Ftl-3 ligand and fragments thereof having biological activity, one skilled in the art at the time of the invention could readily have produced chimeric proteins having all of the limitations of the claims.

27. The rejection of Claims 1 and 22 under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (Molec. Ther. 3:368-374 (Mar 2001)) as applied to claim 1 and further in view of Sandee et al. (BMC Biotechnology 2:16-23 (2002)) is maintained.

Applicant's arguments filed on p. 22 of the Response of 1/18/07 have been fully considered but they are not persuasive. Applicant's allege that Wu does not disclose a purified chimeric protein comprising the Ftl3 ligand and a tumoricidal agent, and inasmuch as Sandee discloses a tumoricidal antibody, Sandee does not contemplate a fusion protein comprising the Ftl3 ligand.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, and as discussed supra, the chimeric protein is not patentably distinguishable over Wu, and because

Sandee discloses tumoricidal antibodies and linker peptides of $(Gly_4Ser)_4$ being flexible and improving stability of protein domains, one skilled in the art at the time of the invention could readily have produced chimeric proteins having all of the limitations of the claims based on the combined disclosures of the references.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

28. Claims 1-23, 35, 36 and 58-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-23, 35, 36 and 58-67 are indefinite for the recitation "substantially purified" because in Claim 1 the term "substantially" is not defined, nor does the specification provide a sufficient definition for the term. The specification supports art known methods for expressing and purifying a chimeric protein where the result is a substantially homogeneous recombinant protein [0121]. The specification does not define what conditions or limits must be met in order for a protein to be substantially pure. For example, can other materials be present along with the chimeric protein that do not affect the basic and novel characteristics of the chimeric protein, and if so, what would those materials be and what levels or concentrations are permissible? Recombinant cells expressing the chimeric protein into culture media are disclosed.

Thus, an expressed protein in culture medium would be substantially pure compared to for example, a chimeric protein expressed in a transgenic animal. One skilled in the art cannot determine what the metes and bounds are for the phrase "substantially purified."

b) Claims 59-61, 65 and 66 recite improper Markush group language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

29. Claims 1-7, 10, 12-17, 19-23, 35, 36, 50-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (USPN 6,218,371; cited on the 892 form of 7/18/06) in view of Wu et al. (Molec. Ther. 3:368-374 (Mar 2001); cited on the 892 form of 7/18/06) or Hung et al. (Cancer Research. 61:1080-1088 (February 1, 2001); cited on the 892 form of 7/18/06), and further in view of Lynch et al. (US20030113341); cited on the 892 form of 7/18/06), Trefzer et al. (Arch Dermatol. Res. 292:583-589 (2000); cited

on the 892 form of 7/18/06) and Sandee et al. (BMC Biotechnology 2:16-23 (2002); cited on the 892 form of 7/18/06) as evidenced by Antonysamy et al. (Cytokine 12:87-100 (February 2000); cited on the 892 form of 7/18/06).

The interpretation of Claims 1-7, 10, 12-17, 19-23, 35, 36, 50-57 is of record and discussed supra. Claims 58-62 are drawn to a chimeric protein comprising the Ftl3 ligand of SEQ ID NO:2 and where the tumoricidal agent is an antibody, fragments thereof, or an anti-p230 antibody, or where the tumoricidal agent is TRAIL, where the Ftl3 ligand and tumoricidal agent are connected by a peptide. Claims 63-67 are drawn to a chimeric protein where the Ftl3 ligand comprises amino acid residues 28-160 or 28-128 of SEQ ID NO:2 and where the tumoricidal agent is an antibody, fragments thereof, or an anti-p230 antibody, or where the tumoricidal agent is TRAIL, where the Ftl3 ligand and tumoricidal agent are connected by a peptide.

The chimeric protein, a pharmaceutical composition thereof and a kit containing the same for treating a neoplasm in a mammal were prima facia obvious at the time of the invention over Krieg, Wu, Hung, Lynch, Trefzer and Sandee.

Krieg discloses an antigen-cytokine fusion molecule (Col. 3, lines 22-23) where the idiotype of a secreted Ig or a tumor antigen serve as highly specific antigenic molecules for producing a tumoricidal response. The "idiotype" comprises a collection of V-region determinants specific to an antibody (antibody fragments) and the tumor antigen comprises an antigen expressed on a tumor in a subject. In one embodiment, the immunopotentiating cytokine is a protein (fusion protein) consisting of a specific antigen idiotype secreted by a lymphoma fused to the immunopotentiating cytokine

(Col. 9, lines 31-40); an immunopotentiating cytokine is human Ftl3 ligand (Col. 8, line 63- Col. 9, line 1); an idiotype of the 38C13 surface IgM serves as a highly specific tumor-associated antigen (Example 1); purified forms of the fusion or chimeric proteins in the form of a pharmaceutical composition with a pharmaceutically acceptable carrier (Col. 31, lines 13-33).

Wu discloses a fusion protein comprising the soluble form of the human Flt3 ligand (Flex) at the 5' end and the human TNF-related apoptosis-inducing ligand (TRAIL) at the 3' end with or without a peptide linker comprising an isoleucine zipper linking the two moieties (hFlex-zipper-TRAIL (FETZ) or FET, respectively) (p. 369, Col. 1, ¶3; Figure 1); TRAIL induces apoptosis in many human tumor cell lines (p. 368, Col. 2) and is a ligand toxic to tumors (p. 369, Col. 1); hFlex is a hematopoietic factor that stimulates proliferation and differentiation of hematopoietic progentiors (p. 369, Col. 1) and expansion of dendritic cell population (p. 369, Col. 1, ¶3; Figure 7); both FETZ and FET tested on MDA-231 human mammary carcinoma cell line induced cell death as measured by cell viability (p. 372, Col. 1, ¶1-3; Figures 5-7). The ability of Flt3 ligand to stimulate proliferation of myeloid precursor cells, monocytic cells, macrophages (p. 89, Col. 1, ¶4 and Col. 2, ¶3), B-cells (p. 89, Col. 2, ¶4; p. 90, Col. 2, ¶2), dendritic cells (p. 90, Col. 2, ¶4- p. 92, Col. 2, ¶1) and NK cells (p. 90, Col. 2, ¶3) was already known in the art as evidenced by Antonysamy.

Hung discloses a recombinant chimera of the extracellular domain of Flt3 ligand (FL) linked to human papillomavirus-16 E7 (Abstract); Flt3 ligand induces a growth-stimulatory effect on DC precusors (p. 1080, Col. 2, ¶2); HPV-16 oncogenic protein E7

is expressed in most HPV-cervical cancers (p. 1080, Col. 2, ¶3); vaccine or immunotherapies targeting E7 protein may provide treatments for HPV-associated cervical cacners (p. 1080, Col. 2, ¶3); the signal peptide and extracellular domain of mouse FL prepared by DNA amplification; vaccination of mice with chimeric FL-E7 enhances protection of mice against the growth of TC-1 tumors (p. 1083, Col. 1-2; Figures 4-6); linkage of the FL gene to an antigen gene may greatly enhance the potency of DNA vaccines and can potentially be applied to other cancer systems with known tumor-specific antigens (p. 1087, Col. 1, ¶6).

Lynch discloses that the Flt3 ligand is known to affect hematopoietic stem and progenitor cells, and can potently stimulate the generation of downstream or intermediate cells such as myeloid precursor cells, monocytic cells, macrophages, B cells and dendritic cells [0007]; a combination therapy comprising the Flt3 ligand and one or more therapeutic agents [0008] including tumoricidal antibodies such as 4-1BB [0012]; proteins encompassed by amino acids 1-235 of SEQ ID NO:2 as well as proteins having a high degree of similarity or identity with the amino acid sequence of SEQ ID NO:2, and which are biologically active and soluble, or truncated proteins comprising primarily the extracellular portion of the protein, and which retain biological activity and are capable of being secreted. Specific examples of soluble proteins are those comprising amino acids 28-160 of SEQ ID NO:2 [0019]; soluble mammalian Flt3 ligand proteins comprising amino acids 28-182 of SEQ ID NO:2 [0024]; Flt3 ligand comprising amino acids 28 to Xaa of SEQ ID NO:2, where Xaa is an amino acid from 160 to 235 (Claim 12); antibodies reactive to 4-1BB which as T-cell co-activating, and

which can be administered in combination with Flt3 ligand to enhance immune response and synergize to produced anti-tumor immune responses by stimulating more than one mechanism or more than one cell population in order to treat cancer [0050].

Trefzer discloses the SM5-1 antibody having been raised in mice first given a human melanoma cell line SMMUneg followed by the human melanoma cell line SMMUpos obtained from a metastatic lesion from the same patient. The SM5-1 antibody stained primary and melanocytic lesions and the Mab is highly selective over other Mabs in recognizing its cognate antigen in melanocytic lesions. Applicants specification defines the SM5-1 antibody as an anti-p230 antibody (see p. 17, [0099]) and that . "The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997). Trefzer discloses the SM5-1 Mab, and one skilled in the art would envisage that the Fc and SMVH regions comprising the molecule of SEQ ID NOs: 28 and 34 (instant Claim 23), would have been inherent to the antibody of Trefzer.

Sandee discloses an anti-hepatocellular carcinoma scFv where the VH and VL domains are linked by (Gly4Ser)4 peptide linker. Sandee discloses that the scFv retains the original antigen binding site, and represents a valuable molecule for targeted delivery of drugs, toxins to a tumor site, and that the molecules can be further

manipulated by genetic engineering to form anti-tumor fusion proteins with additional effector functions (p. 17, Col. 2, ¶1). Sandee teaches that the Gly4Ser)4 peptide linker is flexible and improves stability of the V domains, that a variety of linkers are available, "but the most widely used linker designs have stretches consisting primarily of glycine and serine residues. Hydrophilic properties of serine allow hydrogen bonding to the solvent and glycines provide the necessary flexibility." (p. 19, Col. 2- p. 20, Col 1).

One skilled in the art would have been motivated to have produced and been reasonably assured of success in producing the chimeric protein at the time it was made over Krieg, Wu, Hung, Lynch, Trefzer and Sandee as evidenced by Antonysamy. Kreig, Wu and Hung teach the advantages of using chimeric proteins comprising the Flt3 ligand and a protein or peptide-based tumoricidal agent such as an immunopotentiating antibody or a tumor-associated antigen or a tumoricidal cytokine that results in dual functions in achieving cancer therapy, where for example, Wu discloses that the fusion protein is "a new concept, which provides the rationale for using a ligand toxic to tumor cells fused to an adjuvant such as a cytokine or Flt3 ligand to achieve dual function in cancer therapy (p. 369, Col. 1, ¶3 to Col. 2, ¶1) and the ability of using an isolated, dual-acting recombinant molecule for administration (p. 373, Col. 2). The motivation to produce chimeric molecules of Kreig, Wu or Hung comprising antibodies such a anti-p230 antibody of Trefzer, and Flt3 ligands comprising SEQ ID NO:2 and fragments thereof of Lynch, and chimeric proteins further being linked by spacers comprising (Gly4Ser)4 of Sandee, would have been based on the success of Lynch, Trefzer and Sandee using these reagents in cancer therapeutics or diagnostics

(Trefzer and Lynch) or in constructing chimeric molecules (Sandee) for caner therapeutics. Because Krieg, Wu and Hung disclose the practical and functional utility of FLt3 ligand-based chimeric proteins and success of using an idiotypic antibody or tumor-associated antigen (Kreig) or another cytotoxic molecule (Wu and Hung) as tumoricidal agents to achieve enhanced immunotherapeutic effects in cancer via apoptotic mechanisms, one skilled in the art could have been reasonably assured of success in generating and modifying the chimeric proteins of the Kreig, Wu and Hung with the antibodies of Trfzer, and the Ftl3 ligand fragments of Lynch and the linkers of Sandee.

The instant claims are not drawn to a proteinaceous tumoricidal agent that is distinguished or limited as being directly or indirectly tumoricidal, and therefore, any tumoricidal agent having an indirect anti-tumor, immune eliciting effect as disclosed in Kreig or a direct tumoricidal effect as disclosed in Wu and Hung and further in view of Lynch, Trefzer and Sandee would render the instant claims obvious.

Conclusion

30. No claims are allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER